Effective Health Care Program

Imaging for the Pretreatment of Small Cell Lung Cancer

Executive Summary

Background

Lung cancer is the leading cause of cancer-related mortality, estimated to account for about 27 percent of cancer deaths in the United States in 2015.[1] Small cell lung cancer (SCLC) is an aggressive subset of lung cancer characterized by rapid doubling time, high growth fraction, and early development of metastatic disease. This histologic subset of lung cancer is primarily seen in smokers[2] and comprises approximately 15 percent of all lung cancers.[3] Despite advances in diagnosis, treatment, and management of lung cancer, the 5-year survival rate for SCLC remains dismal at about 6 percent.[1]

Staging involves determining the extent of disease and guides the choice of treatment. SCLC is often staged using the Veterans Administration Lung Study Group (VALSG) system,[4] which classifies SCLC as either "limited stage" or "extensive stage" disease with the following definitions:

- Limited stage disease (LD): Cancer is confined to one hemithorax and may be present in the regional lymph nodes or in ipsilateral supraclavicular nodes, all of which can be encompassed in a safe radiotherapy field.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare. ahrq.gov/reports/final.cfm**.

- Extensive stage disease (ED): Cancer that cannot be classified as LD, such as when contralateral hilar or supraclavicular nodes, malignant

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pericardial or pleural effusions, or distant metastatic disease are present.

The revised AJCC TNM system[5] can also be used; however, it is used less commonly for SCLC than in non-small cell lung cancer. Lung cancers are classified based on the size of the main tumor, whether it has locally invaded other organs/tissues, spread to lymph nodes, and metastasized to other parts of the body. This information is used to assign a stage between I and IV. A higher stage represents more extensive spread.

The National Cancer Institute reported that from 1975–2008, about 70 percent of SCLC cases presented with extensive stage disease, another 21 percent had regional spread such as mediastinal nodal involvement, and only 5 percent were localized (the other 4 percent were unstaged).[6] The most common sites of metastases for SCLC are the liver, adrenal glands, bone, bone marrow, and brain.[7]

Patients with SCLC who have extensive disease at diagnosis have an estimated 5-year survival of only 1 percent.[8] Chemotherapy has been shown to extend overall survival and improve quality of life. Patients with LD are treated more aggressively with concurrent chemotherapy and radiation with curative intent. After completion of first-line therapy, even without evidence of metastases in the brain, prophylactic cranial irradiation has been demonstrated to prolong survival in both LD and ED.

"Standard" staging of SCLC is not a precisely defined term, but may involve numerous investigations including history, physical exam, chest x-ray, chest CT, bone scan, bone marrow aspiration, and/or MRI or CT of the brain. Accurate staging of patients is essential to select the optimal treatment plan that will maximize a patient's chances of survival. On the one hand, overstaging of SCLC risks denies the patient potentially life-saving treatment, while understaging risks subjects the patient to the unnecessary risk of complications from more aggressive treatment. Given the rapid progression of SCLC, timely diagnosis and staging is important; performing potentially unnecessary tests during the diagnostic and staging process could delay treatment initiation, compromising treatment efficacy.

Multidetector computed tomography (MDCT) of the chest is typically the first test performed to diagnose lung cancer. For staging SCLC, additional MDCT images are taken of the abdomen, pelvis, or head to detect distant metastases. MDCT has general strengths of widespread availability, high spatial resolution, and high speed and is particularly useful for evaluating the lungs, airways, bowel, and cortical bone. However, because it is a structural imaging modality, it may not detect early metastatic disease involving sites such as the bone marrow or lymph nodes and is not always able to characterize lesions as benign or malignant based on their morphologic properties. In addition, some patients cannot receive iodinated contrast material due to allergy or renal insufficiency, limiting evaluation for presence of hilar lymphadenopathy, vascular abnormalities, and lesion characterization; for these patients, the sensitivity of CT may be lower.

Positron emission tomography (PET) is an imaging modality that localizes the uptake of a positron-emitting radioisotope in the body. [18F]-fluorodeoxyglucose (FDG) is the most commonly used PET radiotracer. Because FDG-PET identifies anatomic sites that harbor metabolically active malignant areas, FDG-PET helps distinguish malignant tumors from benign nodules or masses. FDG-PET can also uniquely detect metabolically active metastases that have not caused anatomic changes. Because PET images lack anatomic detail, combined PET/CT scanners have been developed so the molecular information from PET can be anatomically localized with CT. As of 2014, PET without a concurrent CT is no longer the state of the art. Even though they are widely used, PET/CT scans are not perfect, and are associated with false negative and false positive results. False negative scans usually result from non-metabolically active sites of tumor or from suboptimal quality studies. False positives scans can occur due to sites of metabolically active infection or inflammation.

Magnetic resonance imaging (MRI) is a structural and functional imaging technique that measures the biophysical properties of tissue. MRI has widespread availability, high spatial resolution, and high soft-tissue contrast resolution; this imaging modality is particularly useful for detection and characterization of lesions within tissues even when subcentimeter in size, as well as for evaluation of the internal architecture of organs/tissues such as the brain, spinal cord, breasts, bone marrow, muscles, tendons, ligaments, cartilage, and other solid organs. Also, functional imaging capabilities such as diffusion-weighted imaging and magnetic resonance spectroscopy may be used to improve diagnostic accuracy. MRI examinations take longer to perform and generally cost more than MDCT, patients with certain types of implanted electronic or metallic devices cannot undergo MRI. Newer devices, including some pacemakers, are increasingly MRI-compatible. Some patients with claustrophobia may have difficulty tolerating an MRI examination. Combined PET and MRI scanners are a recent technical development;

they promise the sensitivity of PET combined with the anatomic detail of MRI.

Endobronchial ultrasound (EBUS) is a bronchoscopic technique utilizing ultrasonography to visualize structures within and adjacent to the airway wall, whereas endoscopic ultrasound (EUS) is an endoscopic technique that uses ultrasonography to visualize structures within and adjacent to the esophageal wall. These techniques are minimally invasive and can be performed on an outpatient basis. EBUS-guided transbronchial needle aspiration (EBUS-TBNA) is generally performed if suspected lymph nodes are in the anterior or superior mediastinum and appear to be accessible based on prior cross-sectional imaging, whereas EUS-guided fine needle aspiration (EUS-FNA) may initially be used for nodes that are paraesophageal or subaortic in location or located in the posterior or inferior mediastinum. EBUS-TBNA can also be used to sample hilar lymph nodes. A typical EBUS procedure for lung cancer staging involves standardized sampling of multiple nodal stations that have >5 mm lymph nodes that are detectable and accessible via the EBUS scope.

Bone scintigraphy is a planar molecular imaging technique with widespread availability, high contrast resolution, and relatively low cost compared with FDG-PET/CT. However, false-negative results can occur since bone scintigraphy only indirectly detects the effects of metastatic lesions upon bone turnover. False-positive results can also occur due to visualization of increased bone turnover caused by non-neoplastic etiologies such as fractures and osteomyelitis.

Regarding patient subgroups, performance of various imaging modalities may be affected by comorbidities such renal insufficiency, which potentially limits use of contrast for MDCT or MRI. Generally, body habitus may limit the diagnostic quality and accuracy for any imaging modality. Many scanners are unable to safely accommodate patients above a particular weight or girth. Tumor characteristics may be associated with comparative accuracy and/or effectiveness.

A 2013 guideline from the American College of Chest Physicians recommended that patients with either proven or suspected SCLC undergo CT of the chest and abdomen or CT of the chest extending through the liver and adrenal glands, as well as MRI of the brain and bone scintigraphy.[9] In patients with limited stage SCLC, PET was also suggested. In 2014, the American College of Radiology (ACR) appropriateness criteria review gave the highest rating of "usually appropriate" (with regard to staging SCLC) to the following specific modalities: CT of the chest and abdomen with contrast, MRI of the head with and without contrast, and FDG-PET/CT from skull base to mid-thigh.[10] Bone scintigraphy was rated as "may be appropriate" and considered unnecessary if PET/CT had been performed.

Scope and Key Questions

The scope of this report is to compare imaging modalities in the context of pretreatment staging for SCLC. The Key Questions (KQs) we addressed were as follows:

KQ 1: What are the test concordance and comparative accuracy of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) for the pretreatment staging of SCLC?

   a. Test concordance

   b. Sensitivity

   c. Specificity

   d. Positive predictive value

   e. Negative predictive value

   f. Positive likelihood ratio

   g. Negative likelihood ratio

KQ 2: When used for the pretreatment staging of SCLC, what is the comparative effectiveness of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) on later outcomes?

   a. Choice of treatment (e.g., surgery, chemotherapy, radiation)

   b. Timeliness of treatment

   c. Tumor response

   d. Harms due to overtreatment or undertreatment

   e. Survival

   f. Quality of life

KQ 3. To what extent are the following factors associated with the comparative accuracy or effectiveness of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) when used for the pretreatment staging of SCLC?

   a. Comorbidities

   b. Body habitus

   c. Tumor characteristics

Note that two terms above, "accuracy" and "effectiveness", are used as overarching labels for different sets of outcomes. The "accuracy" outcomes (which are part of KQ 1), involve an accurate determination of the patient's stage, whereas the "effectiveness" outcomes (which are listed for KQ 2), involve the post-staging outcomes such as clinical management and response to treatment. For comparing the *effectiveness* of two imaging modalities, we required that studies make direct comparisons between two or more modalities, whereas for *accuracy*, we included studies that only used one imaging modality. Our full list of inclusion criteria appear in the section below called "Study Selection".

Methods

Literature Search

With general guidance from the review team, literature searches were performed by medical librarians within the Evidence-Based Practice Center (EPC) Information Center; searches followed established systematic review methods. We searched the following databases using controlled vocabulary and text words: EMBASE, MEDLINE, PubMed, and the Cochrane Library. The complete search strategy is available in the full report. Each article was screened by at least two people using the database Distiller SR (Evidence Partners, Ottawa, Canada). The last search date was June 15, 2015.

For our gray literature searches, we searched for relevant devices on the FDA Web site (i.e., EUS, EBUS, bronchoscopes, CT scanning systems, bone scintigraphy, bone scan). We also browsed ECRI Institute publications including Healthcare Product Comparison Systems reports, Health Technology Forecast and Hotline reports, and ECRI Institute Sourcebase. On the Internet, we searched clinicaltrials.gov, professional organization Web sites for relevant disease information including prevalence statistics, standards and guidelines, and manufacturer information for relevant diagnostic devices. Professional organization Web sites were identified via Google and National Guideline Clearinghouse (NGC) searches for relevant SCLC screening/diagnostic/staging guidelines. These Web sites were browsed for disease-specific information: National Comprehensive Cancer Network (NCCN), Society of Nuclear Medicine, and the American College of Radiology.

Study Selection

Our inclusion criteria are listed below in five categories: Publication criteria, study design criteria, patient criteria, test criteria, and data criteria.

Publication Criteria

a. Full-length articles: The article must have been published as a full-length, peer-reviewed study.

b. Redundancy: To avoid double-counting patients, in instances in which several reports of the same or overlapping groups of patients were available, only outcome data based on the larger number of patients were included. However, we included data from publications with lower numbers of patients when either (1) a publication with lower patient enrollment reported an included outcome that was not reported by other publications of that study, or (2) a publication with lower patient enrollment reported longer followup data for an outcome.

c. Publication date: We included studies published since January 1, 2000. Technical progress in all the imaging modalities under consideration means that older studies are likely to underestimate the diagnostic performance of these modalities.

d. We initially had excluded studies not published in English, but after identifying a relatively low number of qualifying studies, we removed that requirement.

Study Design Criteria

a. The study must have provided data on at least one test of interest. Ideally, studies would directly compare two or more tests (or test strategies). The comparison may also be addressed indirectly by comparing one set of studies of one imaging test and another set of studies of another imaging test (e.g., a set of studies reporting the accuracy of MRI at mediastinal node staging of SCLC compared with a separate set of studies reporting the accuracy of CT at mediastinal node staging of SCLC). This is an indirect comparison of modalities, so conclusions based on it are weaker.

b. For comparisons of variants of a given modality, and studies of patient factors or tumor characteristics for KQ3, the comparison must have been planned in advance.

c. For comparative accuracy (KQ1), the study must have compared both tests to a common reference standard. The reference standard must not have been defined by either imaging test being assessed. We set no requirements on what the reference standard must be (e.g., biopsy, clinical followup).

d. For comparative effectiveness (KQ2), some patients must have received one of the imaging tests (or test strategies), and a separate group of patients must have received a different imaging test (or test strategy).

This design permits a comparison of how the choice of test (or test strategy) might influence choice of treatment, timeliness of treatment, harms due to over/undertreatment, survival, and/or quality of life.

e. For the influence of patient factors or tumor characteristics (KQ3), the study must have reported comparative accuracy data stratified by patient/tumor factor or comparative- effectiveness data stratified by patient/tumor factor.

Patient Criteria

a. The study reported data specifically on patients undergoing staging for SCLC, or if the data were combined with other types of patients, at least 85 percent of the patients in the reported data were undergoing staging for SCLC.

b. Adults. At least 85 percent of patients must have been aged 18 years or older or data must have been reported separately for those aged 18 years or older.

c. Studies of the staging of *primary* SCLC were included. Studies for the staging of *recurrent* SCLC were excluded.

d. Data on imaging tests performed after any form of treatment (e.g., chemotherapy) were excluded, but pretreatment imaging data were considered.

Test Criteria

a. Type of test. Only studies of the imaging tests of interest were included (listed in the KQs above). Studies of CT that did not explicitly specify whether CT or MDCT was used were assumed to be MDCT. Given our publication date of 2000 and later, we believe it is safe to assume that CT performed in such studies was MDCT.

b. PET/CT must have been based on a dedicated PET/CT machine. We excluded studies in which PET and CT were acquired separately and later fused for the following reasons. First, methods for image fusion can vary widely. Since accurate staging relies on accurate localization of the of area of increased FDG uptake, inclusion of less-precise means of combining PET and CT images would underestimate the performance of PET/CT. Second, image fusion is no longer the state of the art in PET/CT, and since this report is intended to guide use of imaging technologies in the future, it should reflect the technology presently in use.

Data Criteria

a. The study must have reported data pertaining to one of the outcomes of interest (see the KQs).

- For test concordance (part of KQ1), this means reporting the number of patients for whom the two tests provided the same or different results.

- For comparative accuracy (part of KQ1), this means reporting enough information to calculate both sensitivity and specificity, along with their corresponding confidence intervals (CIs).

- For comparative choice of treatment (part of KQ2), this means reporting the percentage of patients who received a specific treatment choice for one test or test strategy compared with another test or test strategy.

- For comparative timeliness of treatment (part of KQ2), this means reporting the duration of time elapsed before the initiation of treatment for one test or test strategy compared with another test or test strategy.

- For comparative tumor response (part of KQ2), this means reporting the percentage of patients whose tumor responded to treatment for one test or test strategy compared with another test or test strategy.

- For comparative harms of over- or undertreatment (part of KQ2), this means reporting the percentage of patients who were over- or undertreated (based on authors' judgment) for one test/test strategy compared with another test or test strategy.

- For comparative survival (part of KQ2), this means either reporting median survival after each imaging test or test strategy, mortality rates at a given time point, or other patient survival such as a hazard ratio.

- For quality of life (part of KQ2), this means reporting data on a previously tested quality-of-life instrument (such as the Short Form-36) separately for each imaging test or test strategy.

- For patient factors or tumor characteristics (KQ3), this means reporting data on whether such factors are associated with either comparative accuracy and/or comparative effectiveness.

b. Regarding the minimum patient enrollment, we required data on at least 10 patients per imaging test or test strategy.

c. For all KQs, the reported data must have included at least 50 percent of the patients who had initially enrolled in the study.

Data Extraction and Management

Abstraction forms were constructed in Microsoft Excel, and the data were abstracted into these forms. Elements abstracted include general study characteristics (e.g., country, setting, study design, enrolled N, funding source), patient characteristics (e.g., enrollment criteria, age, sex, final diagnoses including tumor characteristics), details of the imaging methodology (e.g., radiotracer, timing of test, readers, elapsed time between imaging tests, what reference standard was used), risk of bias items, and outcome data. Study methods and outcome data were abstracted by experienced research analysts, in duplicate to ensure accuracy, with discrepancies resolved by consensus. Multiple publications of the same study were grouped as a single study. Duplicates were identified by examination of author names, study centers, patient enrollment dates, and imaging technologies.

Risk-of-Bias Evaluation

For studies directly comparing two or more imaging tests, we applied a set of nine items involving risk of bias (listed in Appendix D). These items were selected from items in the QUADAS-2 instrument,[11] as well as additional items that specifically address bias in the comparison of imaging tests. For studies of only a single imaging test of interest, the critical issue is whether the study's quantitative estimates could be biased, and we used 14 items that are listed in Appendix D (also based largely on the QUADAS-2 instrument.[11] Each study was assessed by two analysts independently, with disagreements resolved by consensus. Once all individual items were resolved, two analysts assigned each study to a risk-of-bias category (low, moderate, or high), with disagreements resolved by consensus.

Data Synthesis

Decisions about whether meta-analysis was appropriate for a particular data set depended on the judged clinical homogeneity of the different study populations, imaging and treatment protocols, and outcomes. When meta-analysis was not appropriate (due to limitations of reported data), the data were synthesized using a descriptive narrative review approach. We avoided specific numerical thresholds for defining clinical importance of differences because the potential clinical impact of a particular difference in test performance varies according to the particular clinical circumstances of each patient case.

Grading the Body of Evidence for Each Outcome

We used the system for grading evidence on diagnostic tests described in the EPC guidance chapter by Singh et al. (2012).[12] This system uses up to eight domains as inputs (study limitations, directness, consistency, precision, reporting bias, dose-response association, all plausible confounders would reduce the effect, and strength of association). The output is a grade for the strength of evidence: high, moderate, low, or insufficient. This grade is provided separately for each outcome of each comparison of each KQ. The grade refers to our confidence in the direction of effect when comparing two imaging technologies, not to the magnitude of the difference between technologies.

A grade was determined separately for each modality comparison (e.g., CT vs. PET/CT). For accuracy, we examined sensitivity and specificity separately. We did not separately grade other accuracy-related outcomes (i.e., predictive values, likelihood ratios) as these grades would be redundant with the grades already assigned for accuracy, since our estimates would be based on the same studies and quantitative syntheses.

A grade of Insufficient was given when evidence did not permit a conclusion for the two modalities being compared with respect to the outcome of interest. For example, if the outcome was comparative sensitivity of CT versus PET/CT, the evidence could support a conclusion that either (1) CT is more sensitive, (2) PET/CT is more sensitive, or (3) the tests are similarly sensitive. If none of these three conclusions could be drawn (as judged by three independent analysts), evidence was graded Insufficient for that comparison. In order to conclude that two modalities differ for an outcome, we used a p value less than 0.05 two-tailed (i.e., the standard value for alpha). In order to conclude that two modalities are approximately equivalent for an outcome, we used the independent judgment of three analysts (with disagreements resolved by discussion).

If the evidence was sufficient to permit a conclusion, the grade was deemed high, moderate, or low. The grade was provided by three independent raters, with discrepancies resolved by consensus. Specifically, each of three analysts considered all strength of evidence domains listed earlier, and decided on a rating for each evidence base, without knowledge of the ratings of the other two analysts. If any of the three ratings differed, a single rating was reached based on consensus discussion.

Peer Review and Public Commentary

Peer reviewers were invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer-review comments on the preliminary draft of the report will be considered by the EPC in preparation of the final report. The dispositions of the peer-review comments are documented and will be published 3 months after the publication of the evidence report.

Results

Our searches identified 2,880 citations, of which we excluded 2,637. The most common reasons for exclusion were: studies of other conditions (e.g., non-small cell lung cancer), studies of treatments, and studies not addressing staging. We retrieved the remaining 243 articles, of which we excluded 236. The most common reasons were: studies with fewer than 10 SCLC patients and studies of other conditions. We included the remaining seven publications. Our search of ClinicalTrials.gov identified no additional relevant ongoing studies.

All seven studies were included for KQ1, and none were included for KQs 2 or 3. Two studies were conducted in South Korea, and one each in Japan, Taiwan, Spain, Germany, and Denmark. The only study not published in English was one from Spain.[13] The studies enrolled a total of 408 patients with SCLC. Of the seven studies, three[14-16] reported the comparative accuracy of two or more tests, and four[13,17-19] reported single-test accuracy. One[16] of the comparative accuracy studies also reported concordance data.

Of the three studies reporting comparative accuracy, we rated two as moderate risk of bias, and one as high risk of bias. The moderate ratings were due to a variety of factors including unknown spectrum bias, failure to report whether test readers had the same clinical information available when interpreting different tests, and the use of test results in determining the reference standard. For instance, Lee et al.[14] assessed the comparative accuracy of bone scan and FDG-PET for bone marrow metastases. However, the study failed to report whether all patients meeting selection criteria during study period were enrolled. Furthermore, study authors did not specify whether nuclear medicine physicians evaluating FDG-PET images for bone marrow metastases had access to results from the prior bone scan, or additional clinical information which could potentially impact their interpretation. In addition, the study did not specify whether both interpreters had access to the same clinical information before interpreting the images.

The one high risk-of-bias rating was assigned due to the above problems as well as the probability of spectrum bias, failure to report the elapsed time between imaging tests, and clear acknowledgement that test readers had non-complementary knowledge. The four single-test accuracy studies were all rated as moderate risk of bias. Reasons for the moderate rating varied across studies, but common problems included failure to account for inter-reader differences and not blinding the reference standard assessment to test results or other clinical information.

Results of Literature Searches

We depict the literature selection process in Figure A. Searches identified 2,880 citations, of which we excluded 2,637 based on abstracts. The most common reasons for exclusion were studies of other conditions (e.g., non-small-cell lung cancer), case reports, studies of treatments, and other studies not addressing staging. We retrieved the other 243 articles, of which we excluded 236. The most common reasons were studies with fewer than 10 patients with SCLC and studies of other conditions.

KQ 1: Concordance and Comparative Accuracy

We first briefly summarize test concordance data, then discuss our findings on comparative accuracy.

Test Concordance

One study[16] reported test-test concordance data for three imaging tests (MDCT, FDG PET/CT, and bone scintigraphy). The data appear in Table C-5 of Appendix C. For various staging determinations (T stage, N stage, pleural effusion, metastases to ipsilateral lung, metastases to contralateral lung, metastases to the liver, metastases to the adrenal glands and metastases to extra-thoracic lymph nodes), authors reported high agreement between MDCT and FDG PET/CT, ranging from 86 percent to 97 percent. For the assessment of osseous involvement, however, agreement was lower (83 percent between MDCT and FDG PET/CT; 46 percent between MDCT and bone scintigraphy; 57 percent between FDG PET/CT and bone scintigraphy). The same study also reported the accuracy of these modalities for the assessment of osseous metastases, and we discuss these data (along with all other accuracy data) in the next section.

Comparative Accuracy

An overview of the included accuracy data appears in Table A. Studies reported many different staging determinations (e.g., whether the patient had limited or extensive disease, whether there was metastasis to the brain), but the evidence for any given determination and

Figure A. Literature flow diagram

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      ╱─────────╲                    ┌──────────────────────────────────────────┐
     ╱  Abstracts ╲                  │ 2,637 excluded                           │
    ╱   screened    ╲ ──────────────▶│ 953: Not SCLC                            │
    ╲               ╱                │ 322: Case report                         │
     ╲             ╱                 │ 269: Treatment study                     │
      ╲─────────╱                    │ 254: Narrative review                    │
           │                         │ 232: Not staging                         │
           │                         │ 170: Screening                           │
           │                         │ 129: Opinion/editor/news/letter          │
           │                         │ 118: None of the modalities of interest  │
           │                         │ 47: Duplicate article                    │
           │                         │ 40: Prognosis                            │
           │                         │ 27: Animals/in vitro/phantom             │
           │                         │ 18: Fewer than 10 patients with SCLC     │
           │                         │ 18: Systematic review                    │
           │                         │ 17: Guideline                            │
           │                         │ 23: Other reason                         │
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│  243 full articles   │
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    ╱  articles     ╲ ──────────────▶│ 64: Fewer than 10 SCLC patients                  │
    ╲  reviewed     ╱                │ 42: Not SCLC                                     │
     ╲             ╱                 │ 31: One test of interest, but no data on staging accuracy │
      ╲─────────╱                    │ 26: No separate SCLC data                        │
           │                         │ 22: Not a study (review, opinion)                │
           │                         │ 10: Unclear whether any patients had SCLC        │
           │                         │ 10: None of the modalities of interest           │
           │                         │ 9: No outcomes of interest                       │
           │                         │ 9: Not staging before treatment                  │
           │                         │ 2: Duplicate of already-identified article       │
           │                         │ 11: Other reason                                 │
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│ 7 studies included,  │
│ all for Key Question 1│
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SCLC = small cell lung cancer

Table A. Overview of included accuracy data		
Staging Determination	**Studies Making Direct Comparisons in Accuracy Between Imaging Modalities**	**Studies Reporting Accuracy Data on a Single Imaging Modality (i.e., for indirect comparisons)**
Limited or extensive disease	Standard staging* vs. FDG PET/CT; 1 study, n=28	Standard staging* only; 1 study, n=25
Presence of metastases to osseous structures (bone or bone marrow)	MDCT vs. Bone scintigraphy; 1 study, n=28 MDCT vs. FDG PET/CT; 1 study, n=29 Bone scintigraphy vs. FDG PET/CT; 2 studies, n=123	Bone scintigraphy only; 1 study, n=76
Presence of lymph node involvement	None	MDCT only; 1 study, n=118 EBUS only; 1 study, n=36
Presence of metastases to adrenal glands	None	MDCT only; 1 study, n=120
Presence of metastases to the liver	None	MDCT only; 1 study, n=120
Presence of metastases to the spleen	None	MDCT only; 1 study, n=120
Presence of any distant metastases	Standard staging vs. standard staging plus FDG PET/CT; 1 study, n=73	None
Presence of metastases to the brain	None	FDG PET/CT only; 1 study, n=21

FDG PET/CT = [18F]-fluorodeoxyglucose positron emission tomography/computed tomography; MDCT = multidetector computed tomography
* The study's definition of "standard staging" involved any of the following: clinical exam, blood test, chest x-ray, bronchoscopy, and bone marrow biopsy.

modality comparison was limited. The largest evidence base involved the comparison of FDG PET/CT to bone scintigraphy for detection of osseous (bone or bone marrow) metastases; this evidence base comprised two studies making direct comparisons (combined n=123) and a single study reporting only bone scintigraphy accuracy data (n=76).

Below, we discuss the results separately for each of eight staging determinations (LD/ED, metastases to osseous structures (bone or bone marrow), lymph node involvement, metastases to adrenal glands, metastases to the liver, metastases to the spleen, any distant metastases, and metastases to the brain). Each of these findings is made even more uncertain by the absence of a consistent and reliable reference method for diagnosis in the studies.

Limited or Extensive Disease

Two moderate risk-of-bias studies[16,18] reported data on the ability of imaging tests to determine whether patients with SCLC had LD or ED. Both reported the use of "standard

staging," which is a combination of multiple testing procedures such as chest x-ray, bone marrow biopsy, and possibly MRI or CT of the brain. In addition, Fischer et al. (2007)[16] reported data on the performance of FDG PET/CT in determining LD/ED. The data suggest that both standard staging and FDG PET/CT had good results (e.g., 86 percent or 95 percent for the sensitivity at detecting ED, and specificity of 90 percent or more at ruling out ED). However, both studies were small (n=28 and n=25, respectively), and the overall data were too imprecise to permit any conclusions about relative accuracy.

Metastases to Osseous Structures (Bone or Bone Marrow)

Three moderate risk-of-bias studies reported data on the accuracy of imaging tests to determine whether patients had metastases to osseous structures (bone or bone marrow). One study compared FDG PET/CT to bone scintigraphy;[14] another study compared CT to FDG PET/CT to bone scintigraphy;[16] the third study provided data

Figure B. ROC plots of accuracy data for osseous metastases
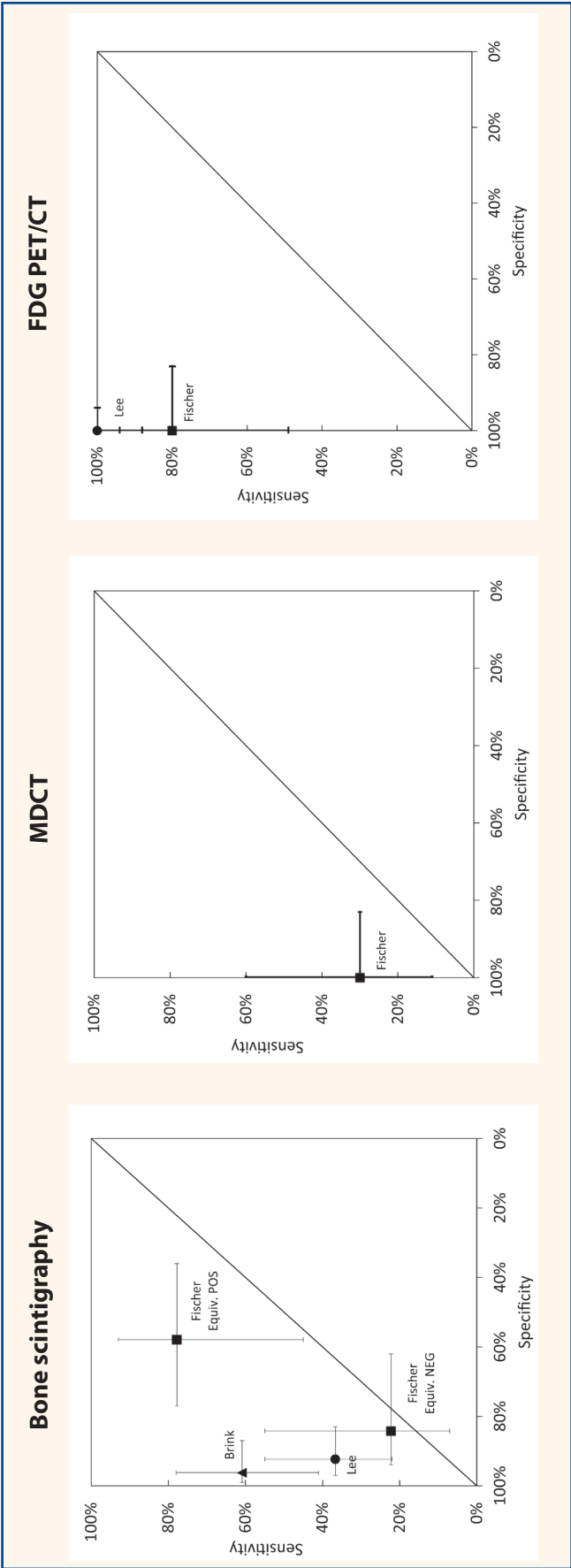
Note: The three plots show the data on osseous metastases in ROC space. The left plot is for bone scintigraphy, the middle plot is for MDCT, and the right plot is for FDG PET/CT. They each show two accuracy measures; sensitivity and specificity. Sensitivity is the percentage of patients who are deemed by the test to have osseous metastases, among those who truly do have osseous metastases. Specificity, by contrast, is the percentage of patients who are deemed by the test to not have osseous metastases, among those who truly do not have osseous metastases. The best possible score for both measures is 100 percent. In each plot, the horizontal axis is specificity (with higher specificity as one moves to the left in the plot), and the vertical axis is sensitivity (with higher sensitivity as one moves up in the plot). The 45 degree line is chance. Thus, an optimal modality would have data in the upper left corner of the plot. Each point is a study (with different studies represented by different shapes). The error bars represent 95% confidence intervals. The study by Brink provided data only on bone scintigraphy, which explains why it does not appear in the other two plots. The study by Lee compared bone scintigraphy and FDG- PET/CT, and the study by Fischer compared all three modalities. The Fischer data are further complicated by the fact that some bone scintigraphy results were considered equivocal by the authors (i.e., neither clearly positive nor clearly negative). Treating equivocal results as positive (as shown with the point labeled "Fischer Equiv. POS") results in higher sensitivity than treating equivocal bone scan results as negative (as shown with the point labeled "Fischer Equiv. NEG"), but lower specificity. For PET/CT, both studies had point estimates for specificity of 100 percent, but the confidence intervals around those estimates were too wide to permit conclusions about relative specificity.

only on bone scintigraphy.[19] The accuracy data are shown in Figure B. For bone scintigraphy, the data from Fischer et al. (2007)[16] are plotted twice: once in which equivocal bone scans are treated as positive tests and a second time if equivocal bone scans are treated as negative tests.

Our statistical tests of these data indicated FDG PET/CT was more sensitive than bone scintigraphy in the Lee study, a finding also replicated by the Fischer study if equivocal bone scans were treated as negative tests. If they were considered positive tests, then FDG PET/CT was more specific than bone scintigraphy for the Fischer study. These are direct comparisons. Considered together with the bone scintigraphy results in the Brink study, we concluded that FDG PET/CT is more sensitive than bone scintigraphy for detecting osseous metastases.

Comparing FDG PET/CT to MDCT, only the Fischer study made a direct comparison, and FDG PET/CT was more sensitive but not more specific. Thus, we concluded that FDG PET/CT is more sensitive than MDCT for detecting osseous metastases.

Finally, turning to the comparison of MDCT with bone scintigraphy, treating equivocal bone scans as positive meant a statistical advantage in sensitivity for bone scintigraphy but a statistical advantage in specificity for MDCT. By contrast, if we treated equivocal bone scans as negatives in Fischer, we found no statistical differences in sensitivity or specificity. Other data on bone scintigraphy from Brink and Lee do not suggest marked differences from MDCT. However, the data were too imprecise to permit any conclusions about the comparison of MDCT and bone scintigraphy with respect to osseous metastases.

Lymph Node Involvement

Two moderate risk-of-bias studies reported data on the accuracy of imaging tests to determine whether patients had lymph node involvement. One study used EBUS for this purpose,[17] and the other used MDCT.[19] The EBUS study reported better accuracy (96 percent sensitivity and 100 percent specificity) than the CT study (70 percent sensitivity, 94 percent specificity). However, patients in the CT study may have been more difficult to assess for lymph node involvement (as not all lymph nodes were histologically assessed), which would bias the comparison against CT. The indirect nature of the comparison precludes conclusions.

Metastases to Adrenal Glands, Liver, or Spleen

A single moderate-risk-of-bias study[19] reported the single-test accuracy of MDCT for detecting metastases to the adrenal glands, liver, or spleen (separate accuracy data for each of these three types). Because such data were not reported for other imaging modalities by this or other studies, we drew no conclusions about how different modalities compare.

Any Distant Metastases

A single high-risk-of-bias study[15] reported the comparative accuracy of standard staging versus standard staging plus FDG PET/CT for detecting any distant metastases. This study's version of standard staging involved history, physical exam, chest x-ray, chest CT, bone scintigraphy, bone marrow aspiration, and either MRI or CT of the brain. The study reported a large difference in sensitivity (92 percent for standard staging plus FDG PET/CT vs. only 46 percent for standard staging), and this difference was statistically significant. The specificities were similar (96 percent for standard staging plus FDG PET/CT vs. 100 percent for standard staging), but the precision was too low to permit a conclusion of equivalence on specificity. We deemed the evidence sufficient to permit the conclusion that standard staging plus FDG PET/CT is more sensitive than standard staging alone for detecting any distant metastases. Given that it was only a single high-risk-of-bias study, we rated the strength of the evidence as low.

Metastases to the Brain

A single moderate-risk-of-bias study[13] reported the single-test accuracy of FDG PET/CT of the brain for detecting brain metastases. Because this and others studies did not report such data for other modalities, we drew no conclusions about how different modalities compare in the assessment of brain metastases.

KQ 2: Comparative Effectiveness

No studies were included for this question.

KQ 3: Factors Associated with Comparative Outcomes

No studies were included for this question.

Discussion

Key Findings and Strength of Evidence

Based on the evidence we reviewed, we concluded the following:

- FDG PET/CT is more sensitive than bone scintigraphy at detecting osseous metastases (Strength of Evidence: low)
- FDG PET/CT is more sensitive than CT at detecting osseous metastases (Strength of Evidence: low)

- Standard staging plus FDG PET/CT is more sensitive than standard staging alone at detecting any distant metastases (Strength of Evidence: low)

Our strength-of-evidence judgments for these conclusions, along with other evidence we identified, but deemed insufficient to permit conclusions, are listed in Table B below. Note that all three of our conclusions involve the superior sensitivity of FDG PET/CT. We discuss this finding below in the section "Implications for Clinical and Policy Decisionmaking."

Implications for Clinical and Policy Decisionmaking

Based on our review of the current evidence, our results suggest two overall conclusions. First, compared with CT and bone scintigraphy (imaging modalities commonly used for staging), FDG PET/CT is more sensitive for detecting osseous metastases in patients with SCLC. Our findings suggest that clinicians evaluating patients for the presence of osseous metastases may consider forgoing bone scintigraphy and routinely using FDG PET/CT instead. Second, for patients with SCLC who have undergone standard staging, the addition of FDG PET/CT increases sensitivity for detecting any distant metastases overall at the patient level.

The evidence base did not allow us to draw conclusions about the comparative specificity of FDG PET/ CT compared with these other modalities; thus, we acknowledge that any of the modalities could yield false positives. If a false positive led to inaccurate "upstaging" to extensive disease, a patient might only receive a palliative regimen instead of aggressive chemotherapy aimed at cure. Unfortunately, as we found only one study evaluating EBUS and no studies evaluating EUS, MRI, or PET/MRI meeting inclusion criteria, we were unable to assess their comparative accuracy with regard to FDG PET/CT.

Our findings regarding FDG-PET are aligned with recent guidelines from the ACR and ACCP: in 2014, the ACR gave the highest rating of "usually appropriate" to the following specific modalities for staging SCLC: CT of the chest and abdomen with contrast, MRI of the head with and without contrast, and FDG-PET/CT from skull base to mid-thigh.[10] Bone scintigraphy was rated as "may be appropriate" and considered unnecessary if PET/CT had been performed. Similarly, the 2013 ACCP guideline recommended a staging workup consisting of CT of the chest and abdomen or CT of the chest extending through the liver and adrenal glands, as well as MRI of the brain and bone scintigraphy. For limited disease patients, the guideline "suggested" FDG-PET" as a replacement for bone scan.

SCLC is an aggressive cancer, and timely staging is important to determine treatment decisions based on whether patients have limited or extensive disease. Currently, as part of the standard staging process, patients may undergo bone scintigraphy, CT of the abdomen and pelvis, brain MRI, and FDG PET/CT. Reducing the total number of tests may improve the timeliness of staging and permit faster initiation of treatment.

Higher sensitivity also has other potential important implications for patient care. First, better detection of metastases can improve patient selection for optimal therapy. The higher sensitivity of FDG PET/CT would provide clinicians more confidence to offer a comprehensive stage-based treatment plan. Second, earlier detection of extensive disease allows patients to be spared from more aggressive concurrent chemotherapy and radiation protocols used for patients with limited disease. Earlier initiation of palliative measures may result in improved quality of life, an important consideration given the current poor prognosis of this disease. Third, improved sensitivity and timeliness of staging may potentially improve the ability of ongoing research trials to prognosticate and detect therapeutic efficacy.

Finally, our results suggest potential resource implications. Although FDG PET/CT may be more expensive than CT and bone scintigraphy, some patients may undergo all three tests when being evaluated for osseous and other distant metastases outside the brain. Eliminating routine use of bone scintigraphy from SCLC staging protocols in favor FDG-PET/CT could potentially result in some cost savings.

Research Gaps

For characterizing gaps, we used the EPC framework proposed by Robinson et al. (2011).[20] This system suggests that reviewers identify a set of important gaps and determine the most important reason for each gap. Each gap should be assigned one of the following reasons for the inability to draw conclusions:

a. Insufficient or imprecise information: no studies, limited number of studies, sample sizes too small, estimate of effect is imprecise

b. Information at risk of bias: inappropriate study design; major methodologic limitations in studies

c. Inconsistency or unknown consistency: consistency unknown (only 1 study); inconsistent results across studies

Table B. Strength of evidence grades

Staging Determination	Test Comparison	Number of Studies and Number of Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Magnitude of Effect	SOE Grade*	Conclusion
LD vs. ED	Standard staging† vs. FDG PET/CT	Direct comparison: 1 study[16] of 28 patients. Indirect comparison: 1 study[18] of standard staging of 25 patients	Moderate	Mixed	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Osseous metastases	FDG PET/CT vs. bone scintigraphy	Direct comparison: 2 studies[14,16] of 123 patients. Indirect comparison: 1 study[19] of bone scintigraphy of 76 patients	Moderate	Mixed	Consistent	Imprecise	None suspected	Large	Low	FDG PET/CT more sensitive
Osseous metastases	CT vs. FDG PET/CT	Direct comparison: 1 study[16] of 29 patients	Moderate	Direct	Unknown	Imprecise	None suspected	Large	Low	FDG PET/CT more sensitive
Osseous metastases	CT vs. bone scintigraphy	Direct comparison: 1 study[16] of 28 patients. Indirect comparison: 1 study[19] of bone scintigraphy of 76 patients	Moderate	Mixed	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Lymph node involvement	CT vs. EBUS	Indirect comparison: 1 study[19] of CT of 118 patients, and 1 study[17] of EBUS of 36 patients	Moderate	Indirect	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Metastases to adrenal glands	CT vs. anything else	Indirect comparison: 1 study[19] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA
Metastases to liver	CT vs. anything else	Indirect comparison: 1 study[19] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA

Table B. Strength of evidence grades (continued)

Staging Determination	Test Comparison	Number of Studies and Number of Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Magnitude of Effect	SOE Grade*	Conclusion
Metastases to spleen	CT vs. anything else	Indirect comparison: 1 study[19] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA
Any distant metastasis	Standard staging† vs. standard staging† plus FDG PET/CT	Direct comparison: 1 study[15] of 73 patients	High	Direct	Unknown	Imprecise	None suspected	Large	Low	Standard staging† plus FDG PET/CT more sensitive
Metastases to brain	FDG PET/CT of the brain vs. anything else	Indirect comparison: 1 study[13] of FDG PET/CT of 21 patients	Moderate	Indirect	Unknown	Imprecise	None suspected	Unknown	Insufficient	NA

EBUS = endobronchial ultrasound; ED = extensive stage disease; FDG PET/CT = [¹⁸F]-fluorodeoxyglucose positron emission tomography/computed tomography; NA = not applicable

since evidence was insufficient to permit a conclusion for this staging determination for this test-test comparison; SOE = strength of evidence

* The SOE grade indicates our confidence in the conclusion about the direction of the effect, not about the magnitude of the difference.

† "Standard" staging of SCLC is not a precisely defined term, but may involve numerous investigations including history, physical exam, chest x-ray, chest CT, bone scan, bone marrow aspiration, and/or MRI or CT of the brain.

d. Not the right information: results not applicable to population of interest; inadequate duration of interventions/comparisons; inadequate duration of followup; optimal/most important outcomes not addressed; results not applicable to setting of interest

We found three primary gaps in the literature on imaging tests for the pretreatment staging of SCLC. The first concerns the dearth of evidence on several tests of interest, particularly MRI, EBUS, EUS, and PET/MRI. This gap exists due to reason a, Insufficient information. Note that we did not restrict our search to studies of particular staging purposes even though some are typically used for specific targets (e.g., brain MRI). EBUS and EUS may be used as much for diagnosis as for staging, which may partially explain the lack of direct evidence on staging SCLC. PET/MRI is a relatively new technology, and we predicted that little would be identified, but future systematic reviews may uncover evidence as it becomes more widespread.

The second gap concerns the absence of study designs to inform the optimal imaging plan for the pretreatment staging of SCLC. Thus, the reason for this gap is reason b, Information at risk of bias. At least three underlying sources exist for the gap: (1) the general lack of direct comparisons of different imaging modalities; (2) the use of mixed reference standards (based on partial histology, other imaging tests, and clinical followup) since not all patients' true stage can be determined before treatment; and (3) the complete lack of studies of comparative effectiveness with patient-oriented outcomes such as management strategy or survival after receiving different test strategies. We recognize that some of these problems are due to the clinical reality that SCLC is fast-growing, necessitating timely initiation of treatment.

The third gap concerns KQ3, which addressed the extent to which comparative accuracy or effectiveness are associated with patient factors (comorbidities, body habitus, tumor characteristics). We identified no studies for this question, so this gap exists due to reason a, Insufficient information. Addressing this problem would be easier than addressing the problems listed in the previous paragraph. Most patient records already contain information on patient characteristics; future research could stratify accuracy results accordingly. Armed with this more detailed data, clinicians and policymakers could possibly recommend tailoring specific strategies for different patient subgroups.

Conclusions

Comparative evidence on the pretreatment staging of SCLC is sparse. We found some low-strength evidence suggesting that FDG PET/CT is more sensitive than CT and bone scintigraphy for assessing osseous metastases, and that standard staging plus FDG PET/CT is more sensitive than standard staging alone at detecting any distant metastases.

References

1. American Cancer Society (ACS). Cancer facts & figures 2015. Atlanta, GA: American Cancer Society (ACS); 2015. 56 p.

2. American Cancer Society. Cancer prevention & early detection facts & figures 2013. Atlanta, GA: American Cancer Society; 2013. 65 p.

3. National Cancer Institute (NCI). Small cell lung cancer treatment (PDQ) health professional version. Bethesda, MD: National Cancer Institute (NCI), National Institutes of Health (NIH); 2014 Feb 21. http://www.cancer.gov/cancertopics/pdq/treatment/small-cell-lung/healthprofessional/page1. Accessed 2014 Jun 11.

4. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer. 2002 Sep;37(3):271-6. PMID: 12234695

5. Rusch VW, Rice TW, Crowley J, et al. The seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Staging Manuals: the new era of data-driven revisions. J Thorac Cardiovasc Surg. 2010 Apr;139(4):819-21. PMID: 20304130

6. Trends in lung cancer morbidity and mortality. Chicago (IL): American Lung Association; 2012 Apr. 34 p.

7. Glisson BS, Byers LA. Pathobiology and staging of small cell carcinoma of the lung. In: Lilenbaum RC, Nicholson A, Jett JR, editors. UptoDate. Waltham, MA: UptoDate; 2013 May 07. http://www.uptodate.com/contents/pathobiology-and-staging-of-small-cell-carcinoma-of-the-lung?source=search_result&search=sclc&selectedTitle=2%7E150#H7. Accessed 2014 Jun 12.

8. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol. 2007 Dec;2(12):1067-77. PMID: 18090577

9. Jett JR, Schild SE, Kesler KA, et al. Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e400S-19S. PMID: 23649448

10. Ravenel JG, Rosenzweig KE, Kirsch J, et al. ACR appropriateness criteria non-invasive clinical staging of bronchogenic carcinoma. J Am Coll Radiol. 2014 Sep;11(9):849-56. PMID: 25086958

11. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003 Nov 10;3(1):25. PMID: 14606960

12. Singh S, Chang S, Matchar DB, et al. Grading a body of evidence on diagnostic tests (AHRQ publication no. 12-EHC079-EF). Chapter 7 of Methods Guide for medical test reviews. AHRQ publication no. 12-EHC017. Rockville, MD: Agency for Healthcare Research and Quality; 2012 Jun 1. http://effectivehealthcare.ahrq.gov/ehc/products/246/558/Methods-Guide-for-Medical-Test-Reviews_Full-Guide_20120530.pdf.

13. Palomar Munoz A, Garcia Vicente AM, Bellon Guardia ME, et al. Is a selective brain (18)F-FDG PET/CT study profitable in patients with small cell lung cancer? Rev Esp Med Nucl Imagen Mol. 2012 May;31(3):124-9. PMID: 21722995

14. Lee JW, Lee SM, Lee HS, et al. Comparison of diagnostic ability between (99m)Tc-MDP bone scan and 18F-FDG PET/CT for bone metastasis in patients with small cell lung cancer. Ann Nucl Med. 2012 Oct;26(8):627-33. PMID: 22729551

15. Sohn BS, Lee DH, Kim EK, et al. The role of integrated 18F-FDG PET-CT as a staging tool for limited-stage small cell lung cancer: a retrospective study. Onkologie. 2012 Aug;35(7):432-8. PMID: 22846975

16. Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol. 2007 Feb;18(2):338-45. PMID: 17060487

17. Wada H, Nakajima T, Yasufuku K, et al. Lymph node staging by endobronchial ultrasound-guided transbronchial needle aspiration in patients with small cell lung cancer. Ann Thorac Surg. 2010 Jul;90(1):229-34. PMID: 20609781

18. Shen YY, Shiau YC, Wang JJ, et al. Whole-body 18F-2-deoxyglucose positron emission tomography in primary staging small cell lung cancer. Anticancer Res. 2002;22(2):1257-64. PMID: 12168935

19. Brink I, Schumacher T, Mix M, et al. Impact of [(18)F]FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging. 2004 Dec;31(12):1614-20. PMID: 15258700

20. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for determining research gaps during systematic reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. http://www.effectivehealthcare.ahrq.gov/ehc/products/201/735/FRN2_Frameworks_20110726.pdf.

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